

alteration. However, the evidence strongly suggests that a critical biosynthetic threshold is required for transdetermination to occur. Still, the authors show that transdetermination requires more than just a generic growth signal and suggest that Wg activity in the weak point performs a special function, providing activation of growth *and* an increase in the developmental plasticity of these cells. Whether the growth activation actually causes increased plasticity is a difficult, but important question for the future.

Is transdetermination relevant to organisms other than flies? The answer to this question is a resounding yes. In a recent paper, Okubo and Hogan report that high levels of Wnt activity in mice cause embryonic cells, already committed to lung fates, to switch to intestinal fates (Okubo and Hogan, 2004). Moreover, transdetermination of the mouse lung precursors to an intestinal lineage occurs only in a subset of cells, in a niche that might be considered the vertebrate equivalent of a “weak point.” In addition to the lung to gut transdetermination, lineage switching and transdetermination have been documented in the epidermis, mammary gland, and prostate in response to increased Wnt activity. Thus Wnt/Wg signaling has special properties that allow these cells to acquire an apparently novel state, similar to “stemness.” Clearly other factors must also play roles in giving the weak point its special attributes, and they remain to be identified. However, Sustar and Schubiger’s findings represent an exciting advance of our understanding of critical events underlying acquisition of pluripotency and will surely provide fuel for the growth of research into stem cell and regeneration biology.

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DOI 10.1016/j.cell.2005.01.022

Phy Tunes: Phosphorylation Status and Phytochrome-Mediated Signaling

Phytochromes are photoreceptors that regulate various aspects of plant growth and development. In this

issue of *Cell*, Ryu et al. (2005) show that PAPP5, a type 5 protein phosphatase, acts on a biologically active phytochrome, increasing its stability and affinity for a downstream signal transducer and thus enhancing plant photoresponses.

Plants rely on different groups of photoreceptors to perceive changes in ambient light conditions and, therefore, to optimize their growth and development according to the ever-changing intensity, quality, duration, and direction of light. Each group of photoreceptors maximally absorbs light in different wavelength regions, triggering diverse cell processes that the plant integrates and translates into physiological and morphological adaptive changes. Phytochromes (phy), the red and far-red light-sensing photoreceptors, are encoded by a small gene family (*phyA–phyE* in the model plant *Arabidopsis thaliana*). All phytochromes exist in two photoconvertible forms, exchangeable from one form into another upon absorption of light. It has been shown that the stability of phyA but not of the other phytochromes is compromised upon activation and that degradation of active phyA occurs within minutes following light treatment (Nagy and Schäfer, 2002). This process, which has been proposed to be a phyA-signaling attenuation mechanism, is mediated by the ubiquitin/26S proteasome pathway and may involve COP1, an E3 ubiquitin-protein ligase that acts as a negative regulator of photomorphogenesis (Seo et al., 2004).

Light activation also promotes translocation of phytochromes from the cytoplasm to the nucleus, where they localize into nuclear bodies (speckles). It has been suggested that these speckles may represent the site of interaction between phytochromes and other factors. In this context, several nuclear phytochrome-interacting proteins have been found to colocalize with phytochromes into speckles, including COP1, the blue-light photoreceptor cryptochrome 2, and PIF3, a transcriptional regulator that controls expression of a number of light-regulated genes. The finding that active phytochromes can interact with DNA bound factors suggests that phytochromes may act directly on transcriptional regulator complexes, thereby allowing immediate transduction of ambient light changes into modulation of gene expression (Martínez-García et al., 2000). In this context, reverse genetic studies have identified a myriad of phytochrome-signaling pathway components, some of them well-known transcriptional factors. The idea of phytochromes interacting with multiple transcriptional regulator complexes and directly or indirectly regulating gene expression is very attractive. In support of this idea, genomic-wide analysis has shown that mutation of just one phytochrome affects the expression of thousands of genes (Ma et al., 2001; Tepperman et al., 2001). Nevertheless, among the downstream phytochrome signaling partners there are also exclusively cytosolic proteins, such as phytochrome kinase substrate 1 (PKS1), suggesting a role for phytochromes in the cytoplasm as well. Others, such as NDPK2, a positive regulator of photomorphogenesis, are located in both the nucleus and in the cytoplasm, where they may interact with phytochromes.

The presence of a Ser/Thr kinase domain in the C

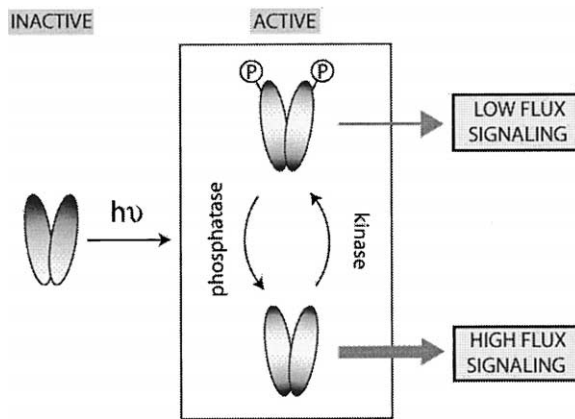


Figure 1. Phytochrome Phosphorylation Status Modulates Its Signaling Activity

Phytochromes are synthesized in their inactive form and are activated upon light absorption. Phosphorylation of active phytochrome, mediated by autophosphorylation activity and/or by yet unknown kinases, attenuates phytochrome-mediated light signaling. Conversely, dephosphorylation of phytochromes, mediated by specific phosphatases such as PAPP5 and FyPP, enhances plant photoresponsiveness.

terminus of phytochromes suggested that these photoreceptors may also phosphorylate specific target proteins. Indeed, several substrates for the kinase activity of phyA have been identified, including, among others, PKS1 and phyA itself (Fankhauser, 2000). Phosphorylation of phyA occurs on specific Ser residues and can be mediated by phyA autophosphorylation activity as well as by yet unknown phytochrome-associated kinases. It has been proposed that phosphorylation of phyA leads to attenuation of plant photoresponses by reducing its affinity for downstream targets (Kim et al., 2004). Therefore, the control of phytochrome phosphorylation status may represent a means for fine tuning the light responsiveness mediated by phytochromes (Figure 1). Reversible protein phosphorylation would imply the action of both specific kinases and phosphatases on phytochromes. Many efforts have been made to elucidate the identity of the enzymes responsible for these activities and their mechanisms of action. For example, recent work described FyPP as a cytoplasmic Ser/Thr-specific protein phosphatase 2A that preferentially binds and dephosphorylates active phytochromes (Kim et al., 2002). The same study proved that variation of FyPP levels results in altered phytochrome-mediated photoresponses related to the initiation of flowering. However, demonstration that specific dephosphorylation of a phytochrome directly affects its signaling activity remained to be obtained.

The aim of a study presented by Ryu and colleagues (Ryu et al., 2005) in this issue of *Cell* is to fill that gap. The authors isolated a type 5 Ser/Thr protein phosphatase, PAPP5, by performing a yeast two-hybrid screen for phytochrome protein interactors. Interestingly, PAPP5 follows a light-dependent distribution when coexpressed with phytochromes, such that PAPP5 is localized in the cytoplasm under dark conditions and is translocated to

the nucleus upon illumination when phytochromes are present. Moreover, in the nucleus, PAPP5 colocalizes with phytochromes into speckles, reinforcing the notion that PAPP5 interacts with phytochromes in vivo. Such interaction was found to yield dephosphorylation of phytochromes in Ser residues important for photoresponsiveness attenuation. In accordance with this result, both binding and dephosphorylation occur preferentially on phosphorylated, biologically active phytochromes. A very interesting finding is that increasing levels of PAPP5 correlate with higher phytochrome-mediated photoresponsiveness. The molecular basis of this phenomenon may be partially explained by the fact that PAPP5 dephosphorylates phyA and, as a result, increases both phyA affinity for its downstream partner NDPK2 and phyA stability upon activation, leading to enhanced photoresponses. Hence, this study reveals a plausible mechanism that allows fine tuning of phytochrome photoresponses at the earliest stage of light signal transduction based on the control of phytochrome phosphorylation status.

Ryu and colleagues' findings (Ryu et al., 2005) raise many intriguing questions about this regulatory mechanism. An important question is how PAPP5 regulates phyB-E activities. The authors report that PAPP5 binds both phyA and phyB and colocalizes into speckles with phyB in vivo, suggesting a role for PAPP5 in the regulation of both phytochromes. However, contrary to the case of the light labile phyA, there is no evidence to support the idea that the phosphorylation status of the phyB-E, which remain stable upon illumination, participates in the regulation of their photoresponsiveness. Moreover, a recent study demonstrated that a truncated version of the phyB molecule lacking the NDPK2-interacting domain and the postulated kinase domain is able to mediate plant photoresponses to red light (Matsushita et al., 2003). This finding suggests that the primary mode of action of phyA and phyB may be different and that, depending on each case, specific dephosphorylation by PAPP5 may result in a different effect on phytochrome activity. The lack of conservation among the different phytochromes of the Ser residues targeted by PAPP5 is another demonstration that further studies are necessary to unveil the molecular processes governing the control of phytochrome phosphorylation status as a means to modulate the activity of each member of the phytochrome family.

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DOI 10.1016/j.cell.2005.01.023